Future of Polypill Use for the Prevention of Cardiovascular Disease and Strokes

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Cardiovascular disease (CVD) remains still the leading cause of death in the United States, and it is estimated to be the leading cause of death in the developing countries by 2020. In addition, the modifiable cardiovascular risk factors (CVRFs), hypertension, hypercholesterolemia, diabetes, and obesity, have increased significantly and by 2020 will account for 80% of all CVD deaths worldwide. Because the CVD and stroke risk increases significantly for subjects aged >50 years, it has been proposed to treat these subjects with a polypill containing 4 to 5 drugs, which is known to reduce the CVRFs for all subjects aged ≥55 years with an estimated reduction of CVD and stroke by 80%. However, this proposal is neither practical nor cost-effective, because it will involve a large number of subjects. Some investigators suggest to incorporate the coronary artery calcium score (CACS) with the Framingham Risk Score (FRS) to reduce the number of subjects who will benefit from the polypill. They have shown that patients with a CACS = 0 at age 50 years will derive no benefit from the polypill regardless of existing CVRFs, whereas those with a CACS of >100 will derive the best benefit. This strategy will reduce the number of qualified subjects for treatment with the polypill by 60%. Greater benefits will be derived with the combination of CACS and FRS. Additionally, other issues will have to be considered before approval of a polypill, and these issues will be discussed in this concise review. In conclusion, a polypill treatment strategy may be effective in the prevention of CVD and stroke, but, to be cost-effective, it may be reasonable to target patients with a high CACS and FRS. **(Am J Cardiol 2014;114:641−645)**

Cardiovascular disease (CVD) remains still the leading cause of morbidity and mortality in the United States and the developed countries[1] and is expected to be the leading cause of morbidity and mortality in the developing countries by the year 2020.[2] In addition, the main cardiovascular risk factors (CVRFs), hypertension, hypercholesterolemia, diabetes, and obesity, which represent 90% of the modifiable CVRFs, have increased significantly in the United States and other countries[1] and by the year 2020 they will account for 80% of all CVD deaths in the developing countries.[2] Also, the decreased CVD burden that has been achieved with the implementation of effective preventive treatment strategies is threatened to be reversed.[3−5] Epidemiologic studies show that the CVD risk begins to increase significantly after the age of 50 years for both men and women worldwide who are free of CVD at the age of 50 years.[6] Therefore, these studies indicate that the treatment for the prevention of CVD should begin by the age of 50 years for both genders. However, the effectiveness of pharmacologic therapy for primary prevention is not yet well established, and several investigators have suggested the use of a polypill in subjects with moderate to high CVD risk. Regarding these issues, a MEDLINE search of the English-language literature was conducted from 2003 (the year of the first polypill publication) to the end of 2013. From this search, 7 pertinent publications using the polypill were selected from 40 abstracts reviewed, and they will be discussed in this concise review together with collateral literature.

Primary Cardiovascular Disease and Stroke Prevention

The concept of using a single polypill for primary CVD prevention has gained significant attention since the original publication by Wald and Law in 2003, who suggested that the daily use of a polypill with 6 component drugs (atorvastatin 10 mg/day or simvastatin 40 mg/day, folic acid 0.8 mg/day, aspirin 75 mg/day, and 1/2 the recommended dose of a thiazide diuretic, a β blocker, and angiotensin-converting enzyme [ACE] inhibitor) could significantly decrease the incidence of CHD and stroke.[7] They estimated that the administration of this polypill in subjects aged >55 years would reduce the blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) and decrease the events from ischemic heart disease and stroke by an estimated level of 88% and 80%, respectively, based on the effects of the component drugs from previous publications.[8−12] The publication of this study created a lot of interest among many investigators and resulted in the design and subsequent publication of 4 randomized studies using polypills with different drug combinations. The findings from these studies, including those from the study by Wald and Law, are summarized in Table 1, and additional data will be provided here.

The study by Yusuf et al[13] was a phase II, double-blind, proof-of-concept trial. The Indian Polypill Study (TIPS)

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See page 645 for disclosure information.

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Table 1
Effects of a polypill on cardiovascular risk factor reduction

Author	Polypill (Drugs)	Patients (no)	Age (yrs)	F-U (wks)	BP (mm Hg)	Change (mm Hg)	LDL-C (mg/dl)	Change (mg/dl)	Projected CHD	Decrease Stroke
Wald & Law[7]	(Statin, aspirin, D, BB, ACEI*)	NA	≥55	NA	150/90	−20/11	186	−70	86%	74%
Yusuf[13]	(Statin, D, BB, aspirin)	412	45−80	12	134/85	−7/6	116	−27	62	48%
Malekzadeh[14]	(Statin, D, ACEI, aspirin)	241	50−79	48	128/79	−5/2	116	−19	34%	21%
Rodgers[15]	(Aspirin, lisinopril, HCTZ, simvastatin)	189	≥18	12	134/81	−10/5	143	−31	60%	50%
Wald[16]	(Amlodipine, HCTZ, losartan, simvastatin)	84	51−77	12	143/86	−18/10	143	−54	72%	64%

ACEI = angiotensin converting enzyme inhibitor; BB = beta-blocker; D = diuretic; F-U = follow-up; HCTZ = hydrochlorothiazide; NA = not available.
* Indicates that ACEI, BB, and D were given at 1/2 their recommended doses.

Table 2
CHD and CVD event rates and 5-year NNT for each polypill study

	Wald & Law[7]			TIPS[13]			Poly-Iran[14]			PILL Collaboration		
CAC scores	Zero	1−100,	>100	Zero,	1−100,	>100	Zero,	1−100,	>100	Zero,	1−100,	>100
Patients (n)	1718	1324	1374	1312	581	345	1241	628	409	1596	1361	1154
(%)	(38.9)	(30)	(31.1)	(58.6)	(26)	(15.4)	(54.5)	(27.6)	(17.9)	(40.8)	(29.7)	(29.5)
CHD events (%)	23 (1.3),	46 (3.5),	106 (7.7)	11 (0.8),	19 (3.3),	31 (9.0)	12 (1.0),	18 (2.9),	33 (8.1)	19 (1.2),	44 (3.8),	96 (8.3)
CHD event												
Rate (1000 pr-yrs)	1.9	5.1	11.6	1.2	4.6	13.3	1.3	4.1	12.0	1.7	5.5	12.5
CVD events	45	75	148	23	25	42	22	26	43	45	67	130
(%)	(2.6)	(5.7)	(10.8)	(1.8)	(4.3)	(18.4)	(1.8)	(4.1)	(10.5)	(2.8)	(5.8)	(11.3)
CVD event												
Rate (1000 pr-yrs)	3.7	8.3	16.5	2.5	6.1	18.4	2.5	6.0	15.8	4.0	8.5	17.2

Constructed from data by Bittencourt et al.[17]

Table 3
Hazard ratios (95% CI) for CHD and CVD events according to CAC score in the 4 polypill studies

Study	Wald & Law[7]		TIPS[13]		Poly-Iran[14]		PILL Collaboration	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
CHD events								
CAC = 0	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
CAC 1−100	2.3 (1.4−3.8)	=0.002	2.7 (1.2−5.8)	=0.014	2.4 (1.1−5.1)	=0.022	2.8 (1.6−4.8)	<0.0001
CAC >100	4.7 (2.9−7.6)	<0.0001	6.4 (2.9−13.8)	<0.0001	5.9 (2.8−12.2)	<0.0001	5.6 (3.3−9.5)	<0.0001
CVD events								
CAC = 0	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
CAC 1−100	1.9 (1.3−2.7)	=0.0001	1.7 (0.9−3.1)	=0.076	1.9 (1.1−3.4)	=0.031	1.8 (1.2−2.7)	=0.002
CAC >100	3.3 (2.3−4.7)	<0.0001	4.4 (2.4−7.8)	<0.0001	4.2 (2.4−7.4)	<0.0001	3.3 (2.3−4.8)	<0.0001

The results were adjusted for age, sex, race, education, and MESA site.
Constructed from data by Bittencourt et al.[17]

included 2,053 Indian subjects aged 45 to 80 years, free of CVD at baseline and with 1 CVRF that included hypertension (systolic BP >140 mm Hg or diastolic BP >90 mm Hg, smoking within the past 5 years, waist/hip ratio >0.85 for women and >0.90 for men, LDL-C >120 mg/dl, and high-density lipoprotein cholesterol <40 mg/dl). The objectives of the study were to evaluate the effects of polypill on BP, heart rate, lipids, and 11-dehydrothromboxane B2. The patients were randomized into 9 groups as follows: (1) aspirin 100 mg/day (n = 205), (2) hydrochlorothiazide (HCTZ) 12.5 mg/day (n = 205), (3) simvastatin 20 mg/day (n = 202), (4) HCTZ/ramipril 12.5/5 mg/day (n = 209), (5) HCTZ/atenolol 12.5/50 mg/day (n = 207), (6) HCTZ/ramipril/atenolol 12.5/5/50 mg/day (n = 204), (7) HCTZ/ramipril/atenolol/aspirin 12.5/5/50/100 mg/day (n = 204), (8) simvastatin 20 mg/day (n = 202), and (9) Polycap containing HCTZ/ramipril/atenolol/simvastatin/aspirin 12.5/5/50/20/100 mg/day (n = 412), and they were followed up for 12 weeks. In addition to the data listed in Table 1, the Polycap reduced the total cholesterol by 32.1 mg/dl, the heart rate by 7 beats/min, and 11-dehydrothromboxane B2 by 283.1/mmol creatinine.

The study by Malekzadeh et al[14] was a double-blind, placebo-controlled trial of 475 Iranian subjects aged 50 to 79 years. The objectives of this study were to evaluate the effects and tolerability of a fixed-dose drug combination therapy with a polypill on BP and LDL-C in adults without elevated BP or lipid levels and free of CVD at baseline.

Table 4
Estimate of lifetime risk for CVD and median survival for men and women by aggregate risk factor status at age 50 years

Risk Stratum	Men			Women		
	Lifetime Risk for CVD (95% CI), %			Lifetime Risk for CVD (95% CI), %		
	75 yrs	95 yrs	Med Surv (IQR), yrs	75 yrs	95 yrs	Med Surv (IQR), yrs
Overall	35 (33−37)	52 (49−54)	30 (22−37)	19 (17−21)	39 (37−41)	36 (28−42)
Optimal risk	5.2 (0−12.2)	5.2 (0−12.2)	>39 (32−>45)	8.2 (0−22)	8.2 (0−22)	>39 (28 > 45)
≥1 Risk factor	26 (21−31)	45.4 (38−51)	35 (26−42)	14.6 (11−18)	39 (33−45)	39 (32−44)
1 Major RF	37.6 (34−42)	50.4 (46−55)	30 (23−36)	18 (15−21)	39 (35−43)	35 (28−42)
≥2 Major RF	53.2 (47−59)	68.9 (62−73)	28 (18−35)	37.7 (33−43)	50.2 (45−56)	31 (23−38)

IQR = interquartile range; Med Surv = medical survival; RF = risk factor.
Constructed from data by Lloyd-Jones et al.[6]

These subjects were randomized to a polypill containing aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg, and HCTZ 12.5 mg (n = 241) or to a placebo (n = 234) and were followed up for 12 months. Additional data to Table 1 include a reduction in total cholesterol by 24 mg/dl (p <0.001), triglycerides by 14 mg/dl (p <0.005), blood glucose by 3.1 mg/dl (p = 0.008), and no change in high-density lipoprotein cholesterol.

The study by Rodgers et al[15] was a randomized, double-blind, placebo-controlled trial of a polypill containing aspirin 75 mg, lisinopril 10 mg, HCTZ 12.5 mg, and simvastatin 20 mg. The objectives of the study were to evaluate the effects of the polypill on systolic BP, LDL-C, and tolerability. This study involved 378 adult subjects aged ≥18 years without an indication for any of the component drugs of the polypill, who had an estimated 5-year CVD risk of >7.5%. The subjects were randomized 1:1 to the Red Heart Pill or to identical placebo and were followed up for 12 weeks. In addition to data in Table 1, the polypill decreased total cholesterol by 31 mg/dl (p <0.001) and triglycerides by 18 mg/dl (p <0.001).

The study by Wald et al[16] was a randomized, double-blind, placebo-controlled, crossover trial. The trial included 86 subjects (84 completed) aged >50 years without a history of CVD at baseline. They were randomized 1:1 to the polypill containing amlodipine 2.5 mg, losartan 25 mg, and HCTZ 12.5 mg or to placebo and were followed up for 12 weeks; then, they were crossed over to the other treatment for an additional 12 weeks. Additional data to Table 1 include the placebo-subtracted decrease by the polypill of total cholesterol by 62 mg/dl, triglycerides by 16 mg/dl, apolipoprotein B by 0.4 gm/L, and an increase in high-density lipoprotein cholesterol by 1.2 mg/dl.

The study by Bittencourt et al[17] involved 6,814 patients aged 45 to 84 years from the Multi-Ethnic Study of Atherosclerosis, who were, supposedly, eligible to participate in the treatments used by 4 published polypill studies[7−15] based on their coronary artery calcium scores (CACS) of 0, 1 to 100, and >100. These patients were allocated to these treatment regimens as follows: (1) Wald and Law (n = 4,416), (2) Yusuf et al and TIPS (n = 2,238), (3) Malekzadeh et al and Poly-Iran (n = 2,278), and (4) Rodgers et al and PILL collaboration (n = 3,911), and they were followed up for a hypothetical period of 7.6 years. The objectives of this study were to evaluate the effects the different polypills would have on subjects with minimal or no CVD risk and in those with higher CVD risk, identifying which subjects would benefit with the treatment with a polypill. The expected CHD and CVD event rates of the patients allocated to 4 polypill treatments according to their CACS are listed in Table 2. The overall rates for the CHD events were low for those patients with CACS = 0, ranging from 1.2 to 1.9 per 1,000 person-years, increased by 2.9 to 4.1-fold for CACS 1 to 100, and by 6.0 to 11-fold per 1,000 person-years for CACS >100. Similarly the expected CVD event rates were low for those with CACS = 0, ranging from 2.5 to 4.0 and increased to 6.0 to 8.5 for CACS 1 to 100, and to 15.8 to 18.4 per 1,000 person-years for those with CACS >100 (Table 2). The hazard ratios (95% confidence intervals) for CHD and CVD events for the participants in the 4 polypill studies based on their CACS are listed in Table 3. A sensitivity analysis showed that the number needed to treat (NNT) to prevent 1 CVD event in 5 years for subjects with a CACS = 0 was >50 for all treatment regimens. For those with a CACS 1 to 100 the NNT was <50 and for those with a CACS >100 the NNT was <30. This study suggests that if the CACS and the FRS are combined,[18] they would better identify those subjects who stand to benefit the most from the cardiovascular risk reduction with the polypill.

Secondary Cardiovascular Disease and Stroke Prevention

All the component drugs used in the polypill trials have been shown to reduce the CVD events in secondary prevention studies.[8−12] However, despite the decrease in CVD mortality by approximately 50%, large treatment gaps still exist with respect to the reduction of CVRFs. The third European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE III) study found that the prevalence of smoking, obesity, uncontrolled BP, and elevated cholesterol accounted for 17%, 35%, 56%, and 25% in the incidence of CHD events, respectively.[19] The situation is even worse in the developing countries according to the World Health Organization study on the Prevention of Recurrence of Myocardial Infarction and Stroke (WHO-PREMISE) conducted in 10 low-to-middle income countries.[20] This study revealed that in patients with preexisting CVD and cerebrovascular disease, aspirin, β blockers, ACE inhibitors, and statins were prescribed in

81.2% and 70.6%, 48.1% and 22.8%, 39.8% and 37.8%, 29.8% and 14.1%, respectively. Although the drugs used for secondary prevention are cost-effective in the developed countries, these same drugs may not be affordable in most patients in low-to-middle income countries.[21,22] In this situation, the polypill may have several advantages for secondary prevention by improving drug delivery, increasing adherence to treatment, and providing affordability with the use of generic drugs. A cost-effectiveness analysis in 6 developing countries using 4 generic drugs in fixed combination (aspirin, a calcium channel blocker, an ACE inhibitor, and a statin) indicated a US $746 to $890/quality adjusted life year (QALY) gained for patients with a 10-year absolute CVD risk of >25% and US $ 1,039 to $1,221/QALY gained for an absolute CVD risk of >5% for primary prevention. For secondary CVD risk prevention, the cost was US $306 to $388/QALY gained.[21] This approach is cost-effective and would be "a best buy" according to World Health Organization recommendations.

Potential Problems Regarding the Future Use of the Polypill

Before the polypill is adapted for use in the primary and secondary prevention of CVD and stroke, several issues have to be resolved. These issues include the following. (1) Proof of efficacy and safety long term: since the publication of a 6-drug polypill by Wald and Law,[7] 4 randomized studies of polypills containing 4 to 5 drugs for primary cardiovascular disease prevention have been published showing a moderate reduction of CVRFs with a projected decrease in CHD and stoke from 34% to 72% and from 21% to 64%, respectively (Table 1). (2) Formulation: the pharmaceutical formulation of the polypill containing 4 to 5 drugs would be rather simple, because formulations of 3-drug combination pills already exist and no problems have been detected regarding their bioavailability, pharmacokinetics, or interaction among the component drugs. Tests done with the Polycap showed that the bioavailability of the Polycap was similar to the component drugs, and there was no interaction among the component drugs.[23] (3) Polypill composition: the composition of the ideal polypill remains uncertain at present. In the 4 completed polypill trials, their effects on BP and serum cholesterol were much less than those proposed by Wald and Law.[7] These lesser than expected effects are probably due to patients' lack of compliance and adherence to treatment or to different drug composition of the polypills, and indicate the need for either a careful selection of the component drugs or an increase in their dose. Also, aspirin has shown minimal primary protective effects and an increase in gastrointestinal bleeding from its long-term use[24] and should not be included in the polypill. Similarly, the incorporation of β blockers may cause problems in patients with asthma or chronic obstructive pulmonary disease, and ACE inhibitors could cause cough in some subjects and should be substituted with angiotensin receptor blockers. Therefore, the need for different polypill preparations should be considered. (4) Food and Drug Administration approval: because the polypills will contain drugs already approved by the Food and Drug Administration with proved effects in the reduction of CVRFs, there should be no problem in their Food and Drug Administration approval. The CVRFs affect significantly the life expectancy of men and women, and, therefore, their reduction with treatment could decrease the incidence of CVD and stroke and prolong their life expectancy. In this respect, the polypill has an advantage over a single drug because it addresses several risk factors simultaneously. (5) Patient acceptance: the acceptance and adherence to treatment by the patients depends on several factors that include side effects, ease of administration, costs, and motivation. The latter could be a major problem for healthy asymptomatic subjects for a life-long treatment. (6) Physician acceptance: several studies show that primary care physicians have concerns regarding the use of the polypill for primary prevention, because its value has not been proven as yet. A study by Virdee et al[25] showed that primary care physicians in England have significant concerns about the use of a polypill for primary prevention of CVD, but they are less concerned about its use for secondary CVD prevention. This study indicates that if a population-based polypill strategy is to be implemented successfully, healthcare professionals will need to be convinced of the potential benefits of such a drug-based approach. In contrast, a survey by Viera et al[26] of 952 physicians in the United States showed that they knew of the benefits of the polypill for the prevention of CVD, and 83% indicated that they will "definitely" or "probably" prescribe it for high risk patients, while 62% would do so for moderate CVD risk patients. The results of this study indicate that physicians should be educated about the benefits of the polypill in order to prescribe it.

Discussion

The data presented suggest that the polypill was effective in reducing the major CVRFs, with a significant projected reduction of CVD and stroke. The question is who should take the polypill. It has been demonstrated that for subjects with a previous myocardial infarction or stroke not taking any treatment, the mortality from CVD would be 5% per year for life, and these patients and those aged >55 years stand to benefit the most from the polypill.[7,27] Other investigators[6] have also emphasized the significance of the various preexisting major risk factors in combination with age, and their treatment will significantly decrease the risk for CVD and stroke as well as extend their life expectancy to the age of 75 or 95 years as demonstrated from Table 4. These studies also show that subjects with no major risk factors at the age of 50 years will derive minimal or no benefit at all with treatment with a polypill, in contrast to those with major risk factors who will derive the maximum benefit. Recently, other investigators propose the incorporation of CACS with the FRS,[17] and have shown that subjects with CACS = 0 will derive no benefit with treatment with a polypill, in contrast to subjects with high CACS >100, who will derive the maximum benefit from the treatment, and the NNT will be reduced by 60%. Other issues include the incorporation of ACE inhibitors and β blockers that could cause cough and respiratory problems in patients with asthma, respectively. Therefore, these drugs could not be incorporated in a unique future polypill. Thus, the need for the production of >1 polypill is real. Another concern raised by Wijns and Rubinaru[28] is the potential loss by the polypill of the indispensable life-style modification

measures such as smoking, diet, and exercise. Also, primary care physicians and patients should be educated about the long-term benefits of the polypill in the prevention of CVD and stroke. Regarding the costs of the polypill, a cost-analysis has suggested that by using generic drugs the polypill will be cost-effective.[21] With respect to the cost of CACS, this is fairly reasonable in the United States and Europe, where the cost is €115.[29] The cost of CACS will be lower in the future for developing countries.[17]

Finally, a strategy should be developed for primary prevention. Instead of "treating all subjects at risk," a more targeted approach should be adapted in "treating only subjects with established, albeit subclinical, disease" using the combination of CACS and FRS till the results of large trials, such as the ongoing HOPE-3 trial, become available. These are the personal views of the authors and are subject to change.

Disclosures

The authors have no conflicts of interest to disclose.

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